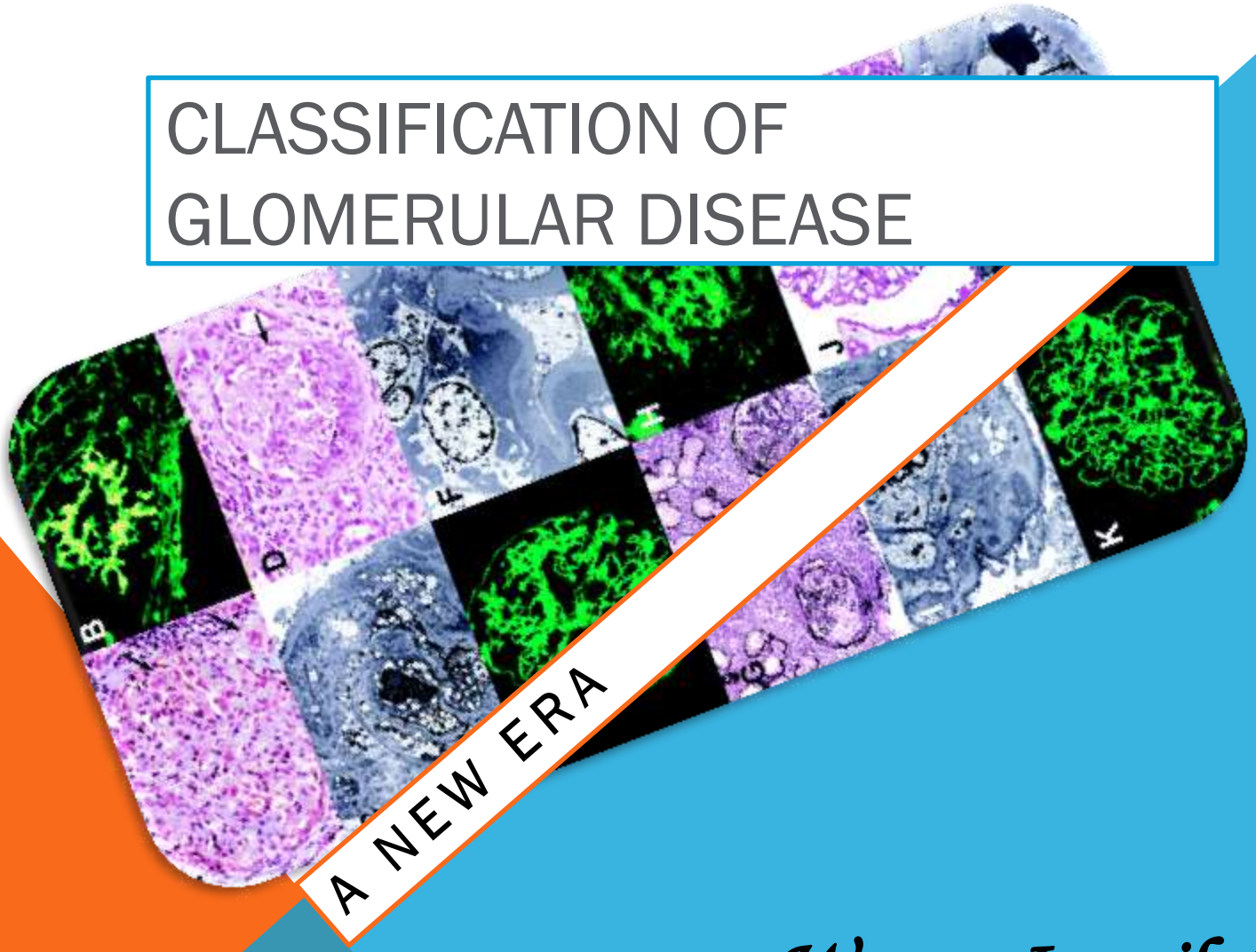
CLASSIFICATION OF GLOMERULAR DISEASE



Wesam Ismail, MD

Pathology department

Beni-Suef University

GLOMERULAR DISEASES

Glomerulonephritis (GN), a complex syndrome encompassing a variety of individual disorders, is associated with significant morbidity and mortality (ESRD, hospitalization or death)

Rare Disease???

Initial estimates of presumed GN incidence and period prevalence in the USA

- GN may be more common than is traditionally appreciated and increase substantially with age
- Type of GN, classified as primary or secondary, is associated with both age and sex
- GN is associated with a substantial hospitalization burden, progression to ESRD, and death
- Tens of thousands of people appear to be affected by GN in the USA alone, making GN an important public health concern

Kidney international. Article in press. July 2016

GLOMERULAR DISEASES

Diseases of the glomerulus although complex have always held a special place of interest for nephrologists

? **Am I missing something?**

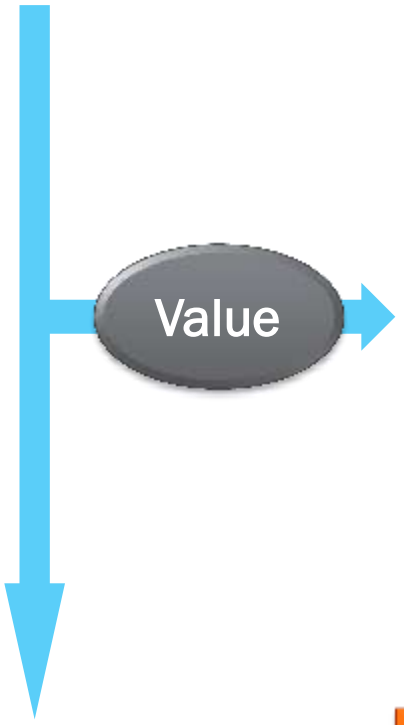
? Should I biopsy?

? If yes, When?

? Should I treat first, then biopsy?

Renal Biopsy

Classifications Based on Renal Biopsy Examination

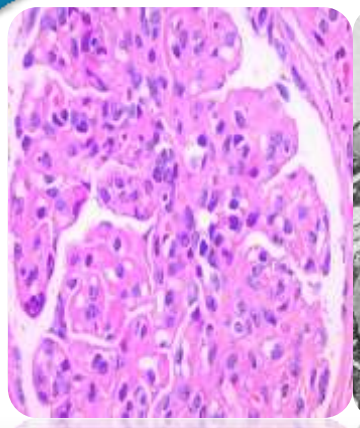


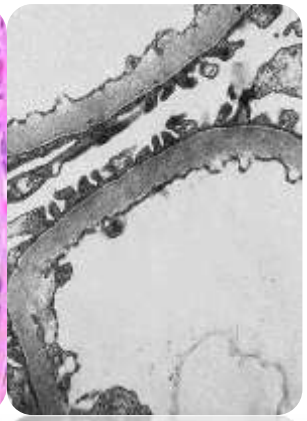
- Unifying the nomenclature *the ability to provide efficient communication between pathologists and between pathologists and clinicians*
- Prognosis *Implement diagnostic information with prognostic indication*
- Facilitate clinical management *guide therapeutic decisions and can be used in the follow-up of the patient*

NOT ONLY for Pathologists

STANDARD HISTOLOGICAL CRITERIA

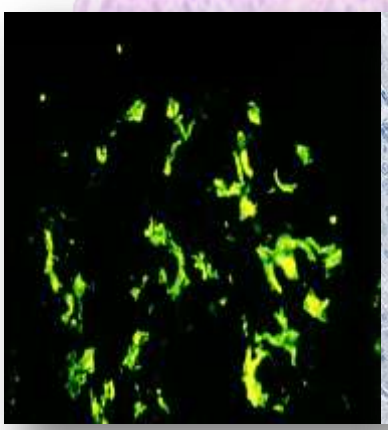
CLASSIFICATIONS





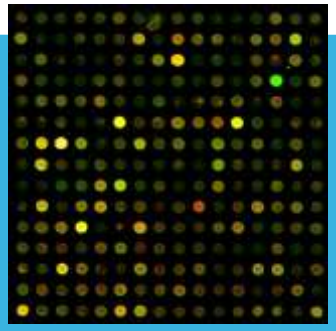
The Past

Pure morphological classifications/patterns



The Present

Based on etiology and pathogenesis



The Future

Gene Expression profiles

Renee Habib
1970s

TABLE I. Classification of Glomerular Lesions (GL)

I. *Pathognomonic Glomerular Lesions*
- Thrombotic Microangiopathy
- Amyloidosis
- Diabetic Glomerulosclerosis
- Tropical 'Membranous' GN
- Lupus Nephritis (with hematoxyphil bodies)

II. *GL in Primary Glomerular Diseases*
- Minimal GL
- Focal GL
  - segmental and focal proliferative GN
  - focal glomerular sclerosis
- Diffuse GL
  - extramembranous GN
  - proliferative GN

from these few exceptions a pathologist should never diagnose a specific disorder from the observation of a particular lesion.

- Systemic Diseases
  - Schönlein-Henoch
  - SLE
  - periarteritis nodosa and necrotizing arteritis
- Mixed Essential I_gG-I_gM Cryo-globulinaemia
- Anti-GBM Nephritis and Goodpasture's Syndrome

IV. *GL in Hereditary Nephropathies*
- Alport's Syndrome
- Nail-patella Syndrome
- Infantile Diffuse Mesangial Sclerosis
- Familial NS
- Partial Lipodystrophy
- Amyloidosis of FMF
- Storage Diseases (Fabry, etc)

V. *Unclassified*

IN > 50 YEARS

Classifying renal disease into etiology, pathogenesis, clinicopathological correlations

1960–present	Immune complex diseases, anti-GBM, lupus nephritis, post-infectious GN, IgAN
1975–present	Focal segmental glomerulosclerosis
1980–present	ANCA disease
1980–present	Membranous glomerulopathy pathogenesis
1990–2009	Hemolytic uremic syndrome
1990–present	Podocyte pathobiology
1990–present	Classification of diseases of the transplanted kidney
1990-present	Amyloidosis

Weening J& Jennette C. Virchows Arch (2012) 461:3–11

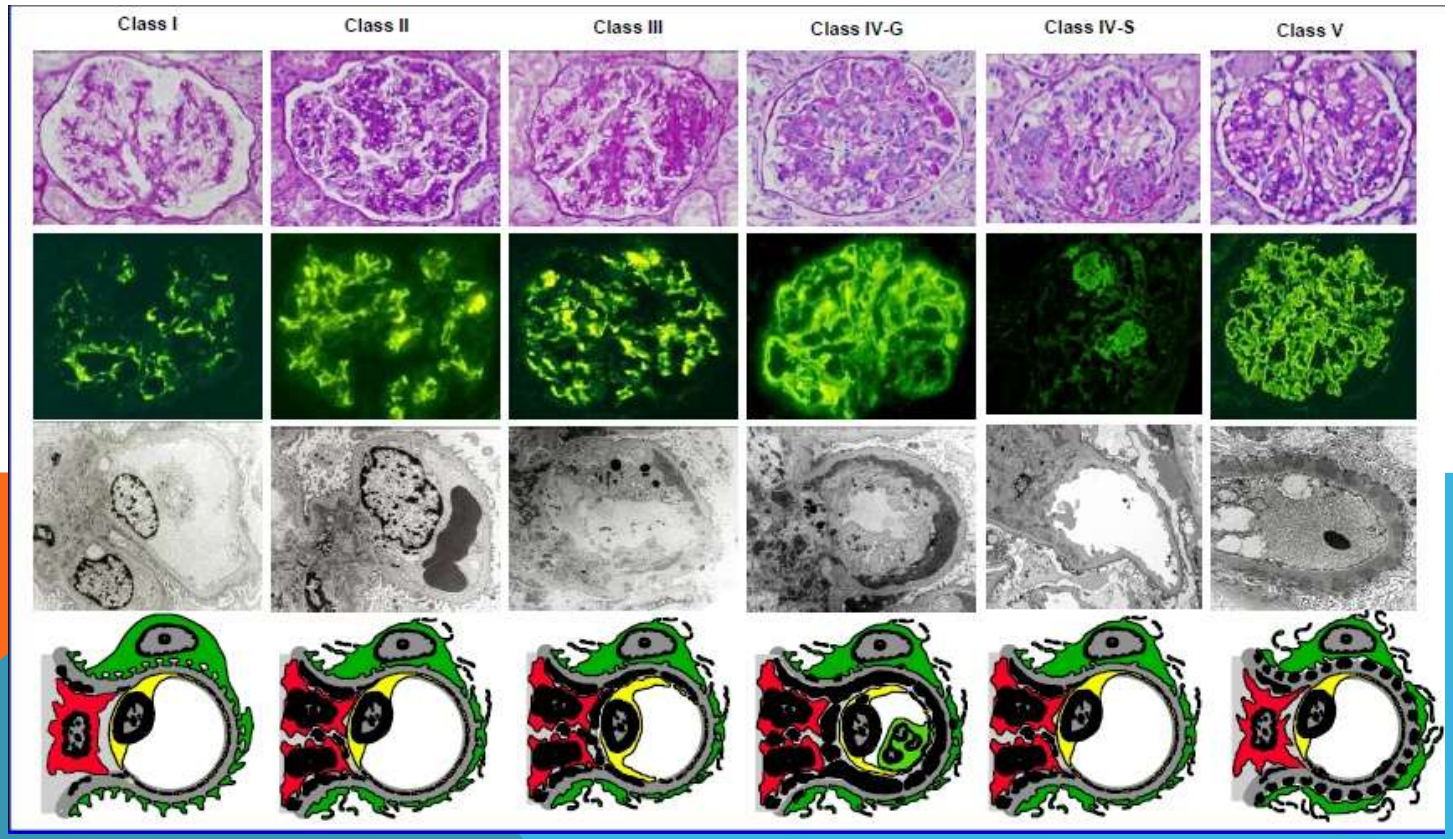
LUPUS GLOMERULONEPHRITIS

McCluskey 1975..... ISN/RPS Classification in 2003

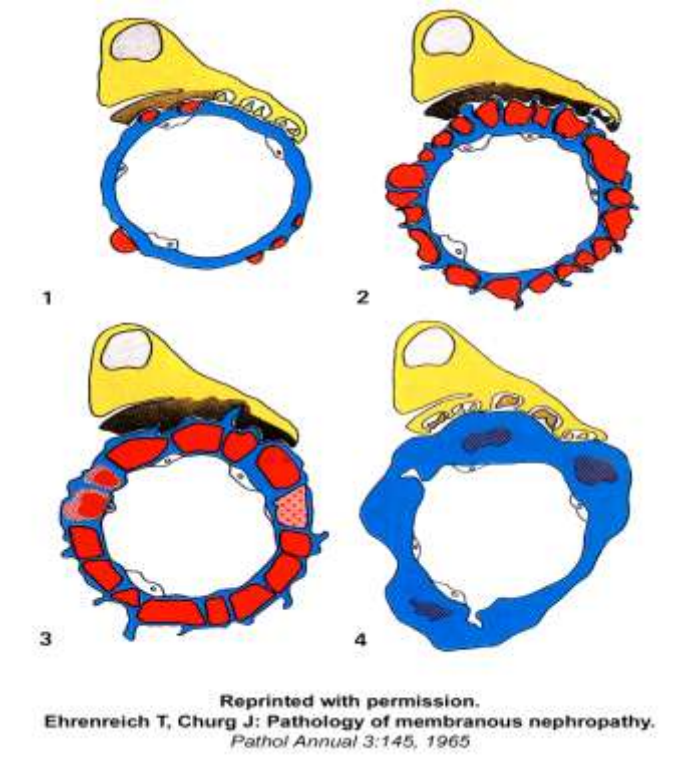
Chronicity & Activity indices

ISN/RPS Classification of Lupus Glomerulonephritis
Columbia 2003

Weening, JJ, D'Agati VD, Schwartz MM et al.
The classification of glomerulonephritis in systemic lupus erythematosus revisited.
Kidney Int 2004, 65: 521–530 and J Am Soc Nephrol 2004, 15 : 241-250.



MEMBRANOUS GLOMERULOPATHY



Neonatal, alloimmune : NEP

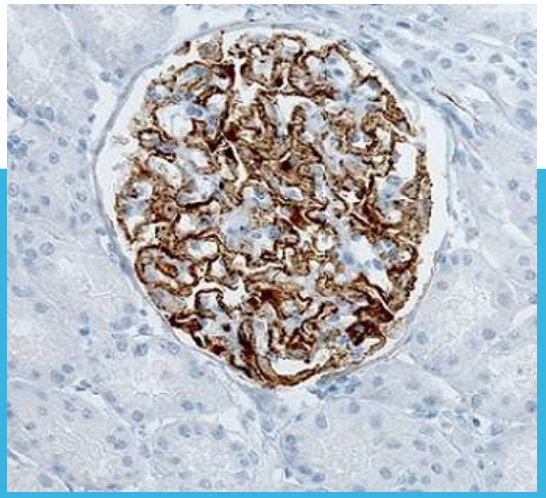
Early childhood MN : BSA

Primary ~~« Idiopathic »~~ MN

- 70-80% : PLA_2R (+ other specificities:AR, SOD2, enolase..?)
- 20-30% : THSD7A,food/environmental Ag (BSA)

« Secondary » MN

Prognostic significance



FOCAL SEGMENTAL GLOMERULOSCLEROSIS

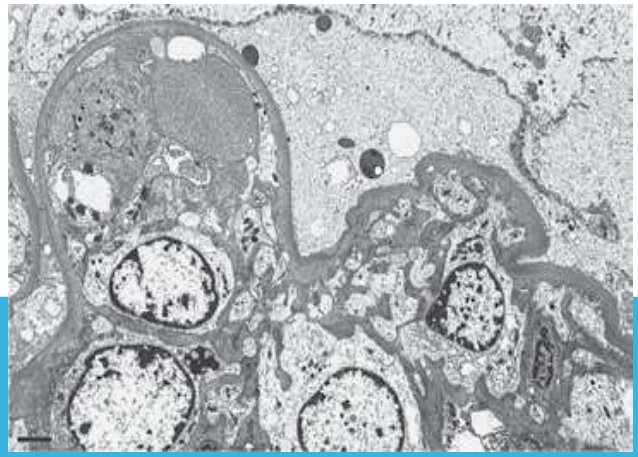
First description by Elema JD et al,*1975*

Better understanding of etiology

Focal segmental glomerulosclerosis is now viewed as a group of clinical–pathologic syndromes

Identification of the podocyte as the major cellular target

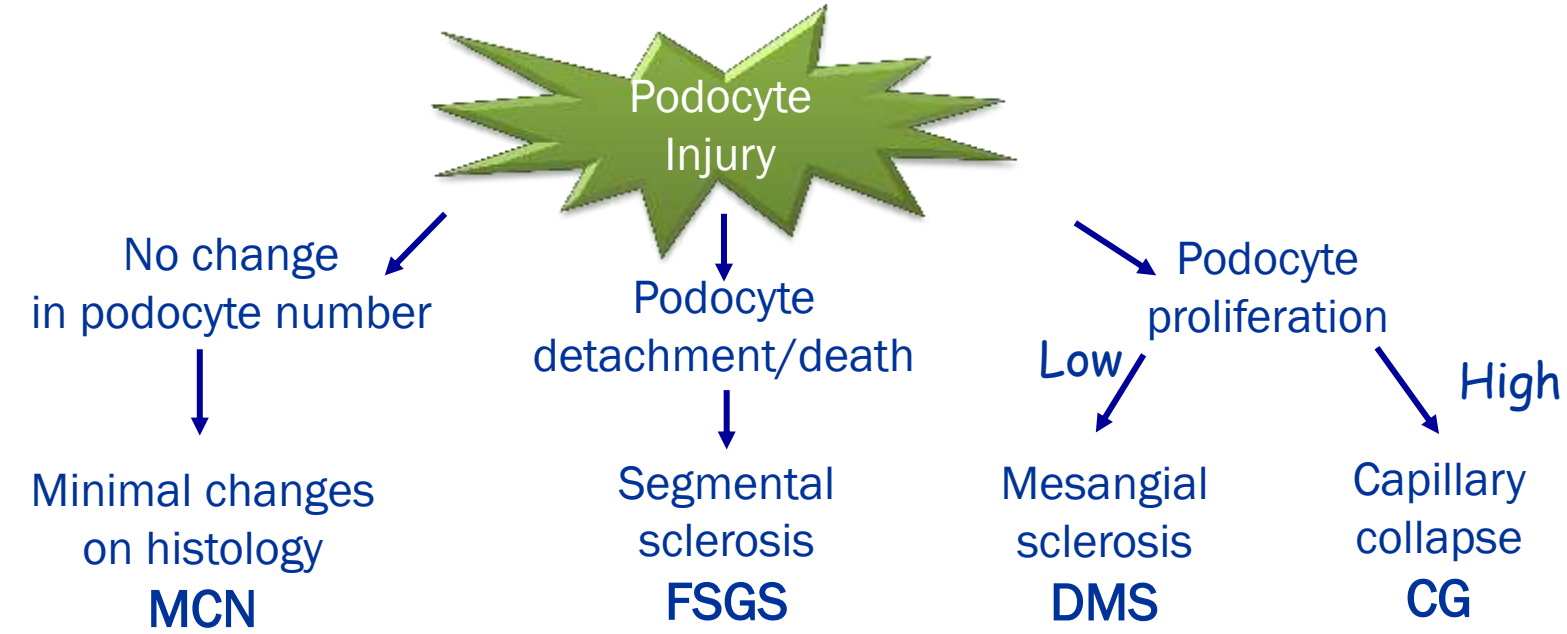
Advances in the field of podocyte biology

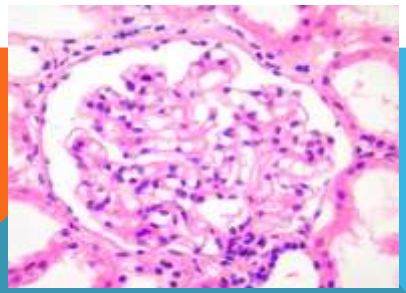


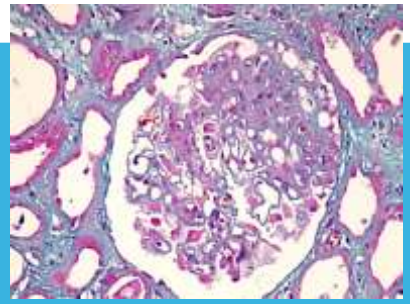
Minimal Change Disease & FSGS

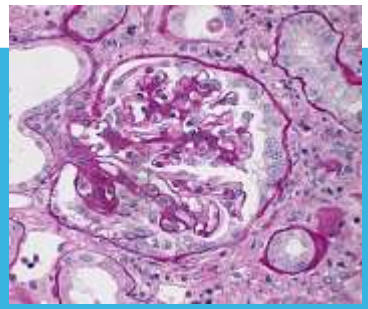
"Podocytopathies"

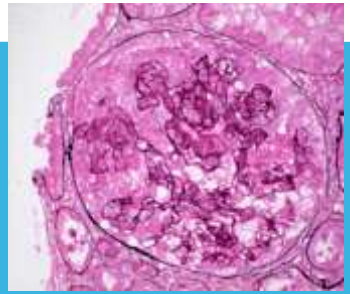
THE SPECTRUM OF PODOCYTOPATHIES











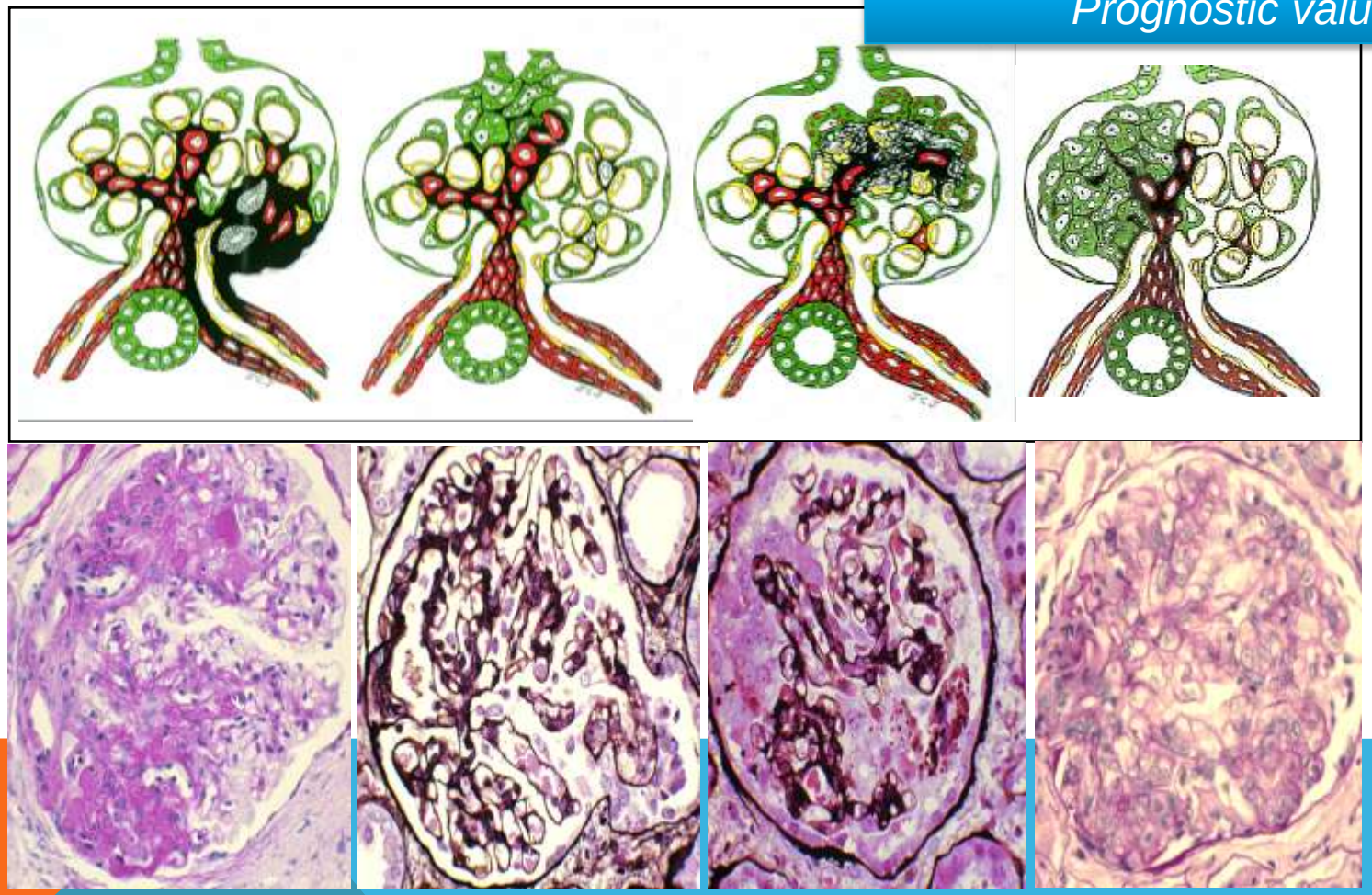
Barisoni et al. CJASN, 2007

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Morphological Classification in 2004

D'Agati et all. Am J Kidney Dis 2004;43

Prognostic value



Perihilar | Tip lesion | Collapsing | Cellular

Courtesy of Charles Jennette

IgA NEPHROPATHY

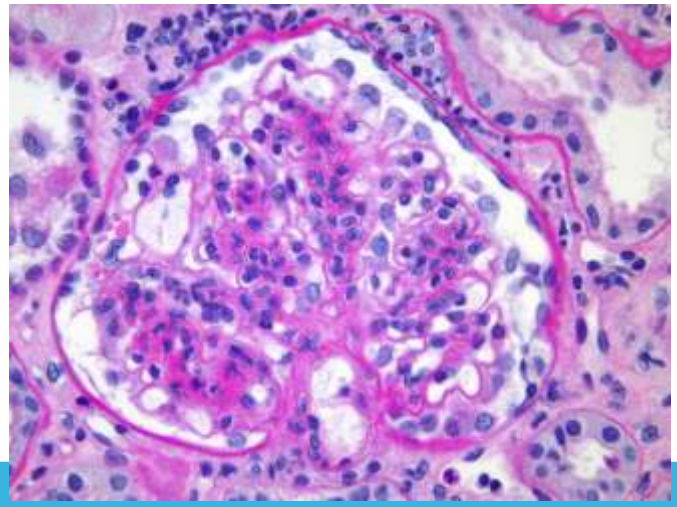
Several Classifications

THE OXFORD CLASSIFICATION (EVIDENCE BASED)

Independent value in predicting renal outcome

Mesangial hypercellularity

- M0: <4 mesangial/cells/area in > 50% of the glomeruli
- M1: ≥4 mesangial cells/area in >50% of the glomeruli



Segmental glomerulosclerosis or adhesion

- S0: absent
- S1 present

Endocapillary hypercellularity

- E0: absent
- E1: present

Tubular atrophy/interstitial fibrosis

- T0: 0-25%
- T1: 26-50%
- T2: >50%

IgA NEPHROPATHY

RECOMMENDED PATHOLOGY REPORT

No Classes eg: I, III, V

1- Detailed description of findings

2- Minimum prognostic data:

Glomerular "pattern":

Mesangial hypercellularity in > or <50% of glomeruli	(M 0/1)
Endocapillary hypercellularity – present/absent	(E 0/1)
Segmental sclerosis/adhesions – present/absent	(S 0/1)
Tubular atrophy/interstitial fibrosis – 0-25%, 26-50%, >50%	(T 0/1/2)

In addition: Total number of glomeruli

Endocapillary proliferation - %

Cellular/fibrocellular crescents - %

Necrosis - %

Global glomerulosclerosis - %

Example: IgA nephropathy showing diffuse mesangial proliferation with focal segmental sclerosis and moderate chronic tubulointerstitial damage (M1,E0,S1,T1)

Diabetic NEPHROPATHY

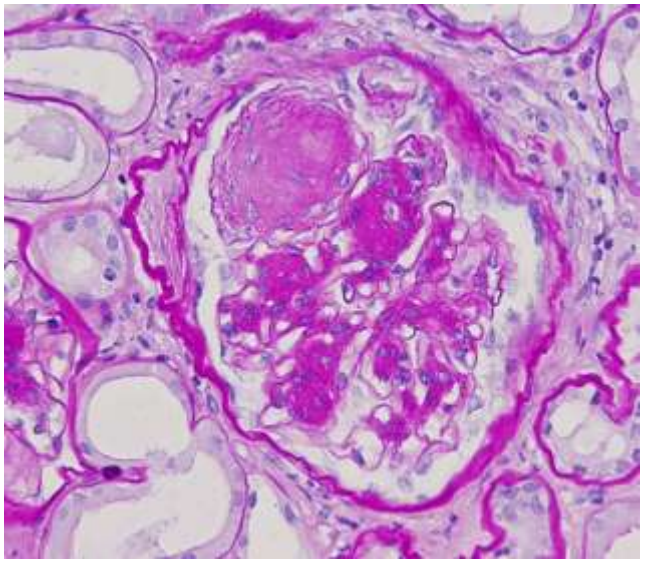
In 1959, Gellman *et al. first reported* findings

Gambara *et al. and Fioretto et al made basic distinctions between typical* and atypical DN

Glomerular diseases superimposed on DN

Podocytopathies

Morphological Classification in 2010 *(Research committee of RPS)*



TERVAERT'S PATHOLOGIC CLASSIFICATION OF DIABETIC NEPHROPATHY

I	Mild or nonspecific LM changes and EM-proven GBM thickening
IIa	Mild mesangial expansion
IIb	Severe mesangial expansion
III	Nodular sclerosis (Kimmelstiel– Wilson lesion)
IV	Advanced diabetic glomerulosclerosis

J Am Soc Nephrol 21: 556–563, 2010

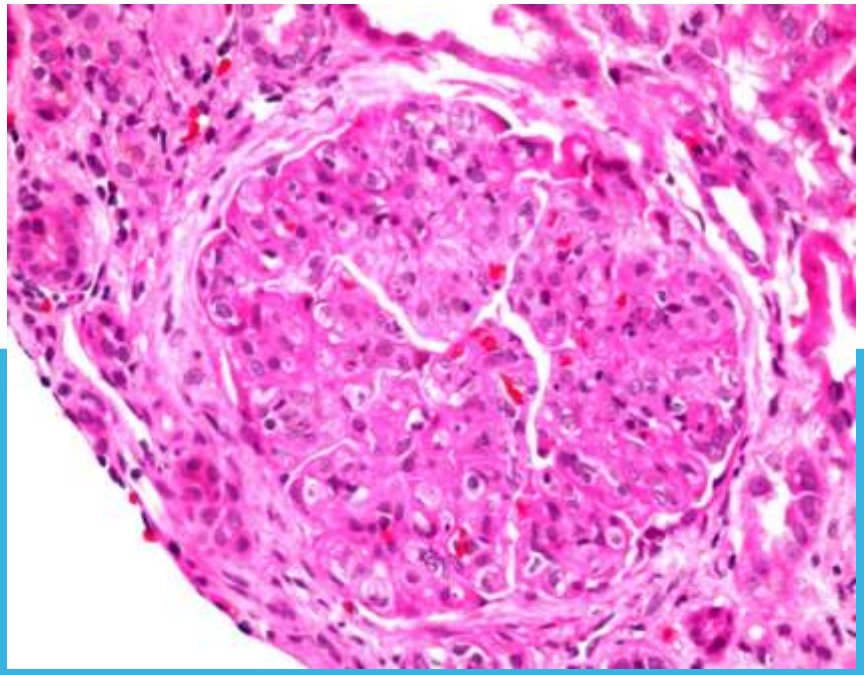
Membranoproliferative GN

Glomerular-injury pattern that is common to a heterogeneous group of diseases

New approach (pathophysiology)

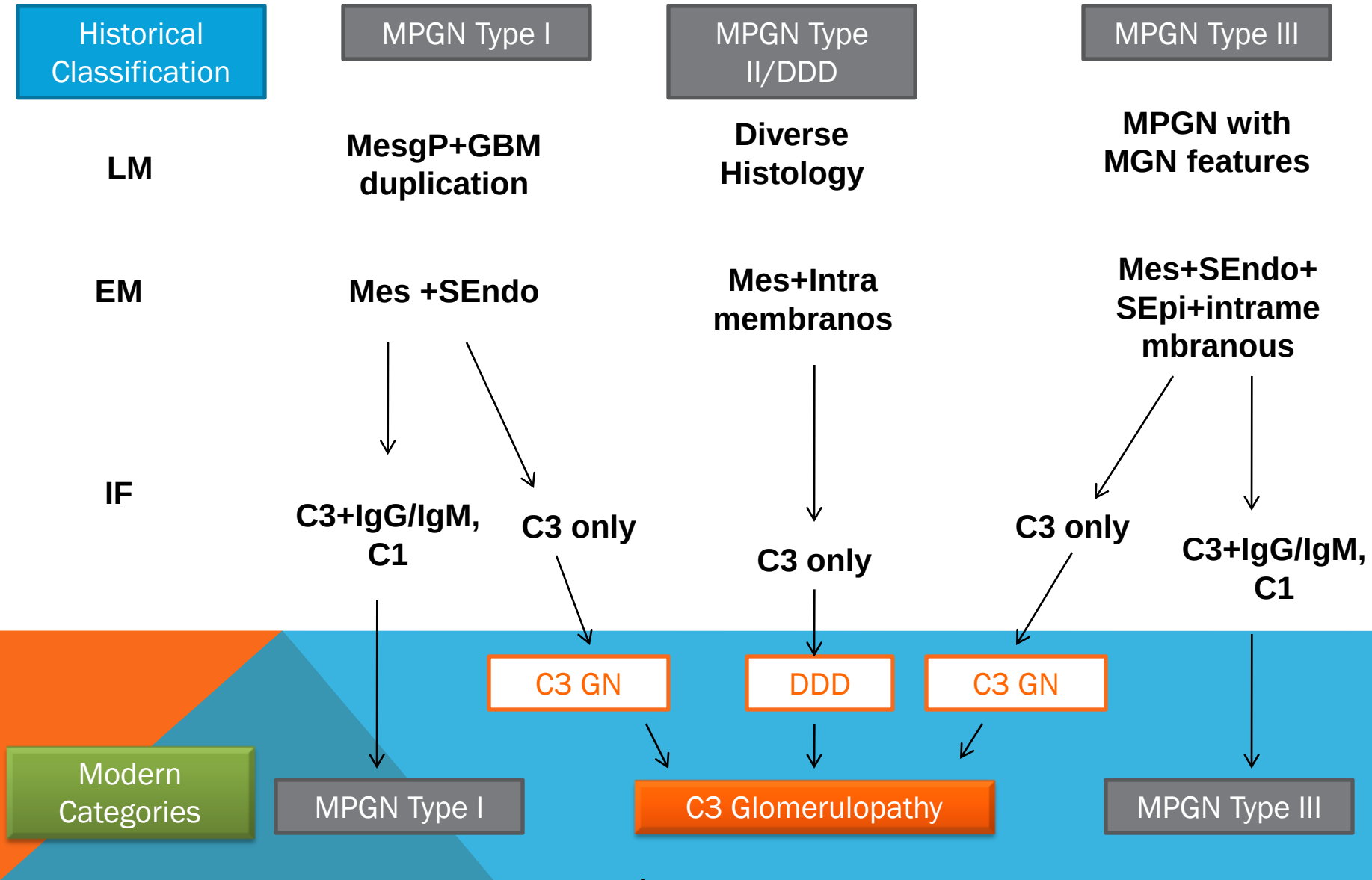
immune-complex–mediated MPGN (increased levels of circulating immune complexes)....HCV, autoimmune dis, MG

complement mediated MPGN (disorders of the alternative pathway of complement).....C3 glomerulonephritis & DDD



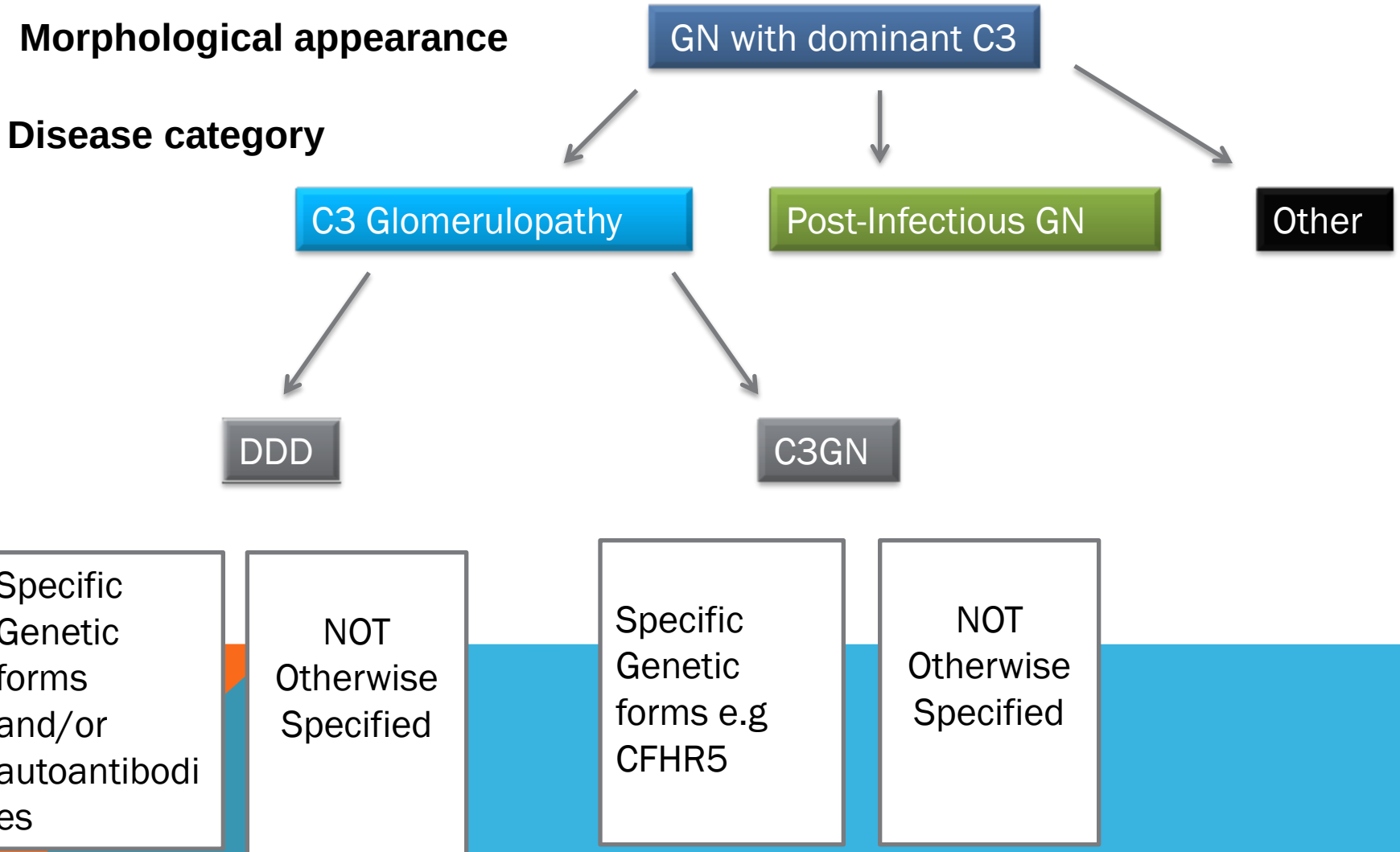
n engl j med 366;12, 2012

MODERN APPROACH



Modified From D' Agati & Bomback. *Kidney International* (2012) 82, 379–381

C3 GLOMERULOPATHY



Adopted from MC Pickering et al.Kidney International (2013)

2012 CHCC Vasculitis Nomenclature

Large Vessel Vasculitis
- Giant Cell Arteritis
- Takayasu Arteritis

Medium Vessel Vasculitis
- Polyarteritis Nodosa
- Kawasaki Disease

Small Vessel Vasculitis
- ANCA-Associated Vasculitis
  - Microscopic Polyangiitis
  - Granulomatosis with Polyangiitis (Wegener's)
  - Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)
- Immune Complex Vasculitis
  - Anti-GBM Disease
  - IgA Vasculitis (Henoch-Schönlein)
  - Cryoglobulinemic Vasculitis
  - Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis)

Variable Vessel Vasculitis (Cogan's, Behcet's, etc.)
Single Organ Vasculitis (cutaneous SVV, primary CNS vasculitis, etc.)
Vasculitis Associated with Systemic Diseases (e.g. Rheumatoid, Lupus, Sarcoid, etc.)
Vasculitis Associated with Probable Etiologies (e.g. HBV, HCV, drug, cancer, etc.)

Jennette et al. Arthritis Rheum 2013;65:1-11

ANCA GLOMERULONEPHRITIS

Highlights

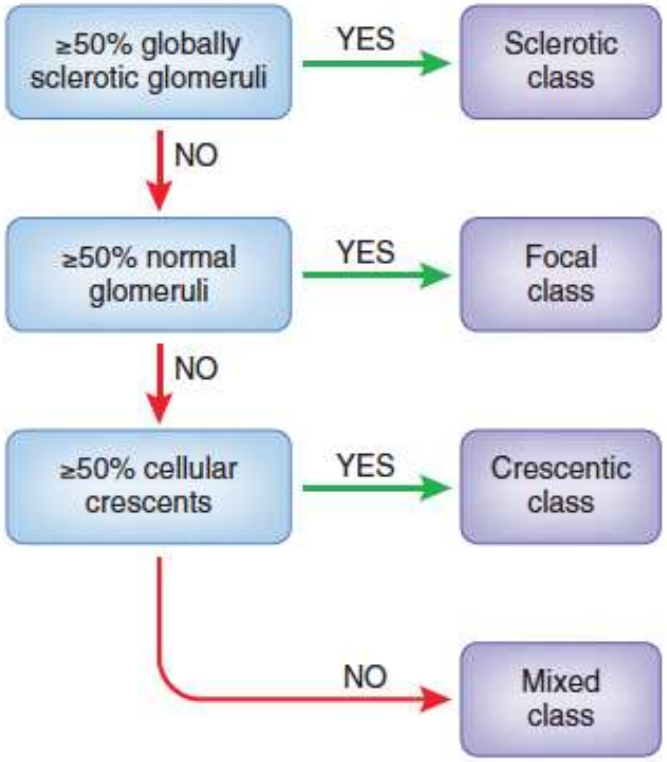


Table 3. Renal outcome according to class

Class	eGFR Entry		eGFR 12 Months		eGFR 12 Months[a]		eGFR 60 Months		eGFR 60 Months[a]	
	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*
Focal	56.4 ± 36.8	16	63.3 ± 23.7	15	1.2 ± 10.6	15	65.6 ± 20.3	11	1.4 ± 11.8	11
Crescentic	11.2 ± 10.9	55	32.8 ± 20.8	40	4.3 ± 17.8	40	39.5 ± 22.5	23	5.2 ± 21.1	23
Mixed	15.4 ± 16.2	16	24.5 ± 21.4	12	−7.3 ± 15.2	12	29.9 ± 16.7	8	−9.5 ± 11.6	8
Sclerotic	10.8 ± 9.5	13	16.6 ± 15.9	8	−12.8 ± 12.4	8	20.4 ± 15.1	4	−14.6 ± 12.1	4

[a]Corrected for entry eGFR.

J Am Soc Nephrol 21: 1628–1636, 2010

MAYO CLINIC/RENAL PATHOLOGY SOCIETY CONSENSUS REPORT ON PATHOLOGIC CLASSIFICATION, DIAGNOSIS, AND REPORTING OF GN

Mayo Clinic/Renal Pathology Society Consensus Report on Pathologic Classification, Diagnosis, and Reporting of GN

Sanjeev Sethi, Mark Haas, Glen S. Markowitz, Vivette D. D'Agati, Helmut G. Rennke, J. Charles Jennette, Ingeborg M. Bajema, Charles E. Alpers, Anthony Chang, Lynn D. Cornell, Fernando G. Cosio, Agnes B. Fogo, Richard J. Glassock, Sundaram Hariharan, Neeraja Kambham, Donna J. Lager, Nelson Leung, Michael Mengel, Karl A. Nath, Ian S. Roberts, Brad H. Rovin, Surya V. Seshan, Richard J.H. Smith, Patrick D. Walker, Christopher G. Winearls, Gerald B. Appel, Mariam P. Alexander, Daniel C. Cattran, Carmen Avila Casado, H. Terence Cook, An S. De Vriese, Jai Radhakrishnan, Lorraine C. Racusen, Pierre Ronco, and Fernando C. Fervenza

*Mayo Clinic, Rochester, Minnesota

J Am Soc Nephrol **27:** ●●●–●●●, 2015

GLOMERULONEPHRITIS

Classification of GN on the basis of etiology/pathogenesis

is primarily on the basis of the findings by immunofluorescence microscopy (IF) or immunohistochemistry (IHC) integrated with light microscopy (LM) and electron microscopy (EM)

The manuscript does not extend to other forms of glomerular diseases, such as membranous nephropathy, podocytopathies, and thrombotic microangiopathy

GLOMERULONEPHRITIS

On the basis of etiology/pathogenesis

Five pathogenic types, each with specific disease entities:

1. Immune-complex GN
2. Pauci-immune GN
3. Antiglomerular basement membrane GN
4. Monoclonal IgGN
5. C3 glomerulopathy

Table 2. Basic format of kidney biopsy report

(1) Specimen type: needle biopsy, wedge, *etc.*

(2) Diagnosis

- Primary diagnosis
  - Disease process/pathogenic type (*e.g.*, IgA nephropathy, lupus GN, ANCA GN, C3 GN)
  - Pattern of glomerular injury (*e.g.*, mesangial proliferative, membranoproliferative, necrotizing/crescentic, and focal and segmental sclerosing)
  - Histologic scores or grade (*e.g.*, Oxford/MEST for IgA nephropathy and ISN/RPS for lupus nephritis)
  - Additional features (*e.g.*, degree of global glomerulosclerosis, IFTA, vascular sclerosis, clinical modifiers, such as cryoglobulin/clinical HCV, bacterial endocarditis/clinical, staphylococcal cellulitis/clinical)
- Secondary diagnoses (list; *e.g.*, acute interstitial nephritis and diabetic glomerulosclerosis); these are not felt to be part of the primary disease

(3) Comment/narrative

- Can be used for summarizing/clarifying morphologic basis of primary and/or secondary diagnoses or clinicopathologic correlations, providing prognostic information, discussing differential diagnosis, and providing appropriate references

(4) Summary of clinical data

(5) Gross description

(6) LM description

(7) IF/IHC

(8) EM

(9) Addendum for special studies

EXAMPLES

Hepatitis C–associated immune–complex GN

Primary diagnosis: immune-complex GN

Pattern of injury: membranoproliferative GN

Additional features: with features of cryoglobulinemic GN (hepatitis C/clinical), focal global glomerulosclerosis (20%), moderate tubular atrophy and interstitial fibrosis (30%),moderate arteriosclerosis, and moderate hyaline arteriolosclerosis

EXAMPLES

Lupus nephritis

Primary diagnosis: (1) lupus nephritis and (2) thrombotic microangiopathy

Pattern of injury: diffuse proliferative and sclerosing GN with focal (10%) cellular crescents

Score/grade: ISN/RPS class IV-G (A/C)

Additional features: thrombotic microangiopathy associated with antiphospholipid antibodies/clinical, focal global glomerulosclerosis (10%), mild tubular atrophy and interstitial fibrosis (10%), moderate arteriosclerosis, and moderate hyaline arteriolosclerosis

EXAMPLES

Infection-related GN

Primary diagnosis: IgA–dominant infection–related GN

Pattern of injury: diffuse exudative GN

Additional features: associated with S. aureus cellulitis infection/clinical, focal global glomerulosclerosis (30%),moderate tubular atrophy and interstitial fibrosis (30%), moderate arteriosclerosis, and moderate hyaline arteriolosclerosis

Secondary diagnoses: diabetic nephropathy, moderate interstitial nephritis

DIAGNOSES

Lupus nephritis

Primary diagnosis: (1) lupus nephritis and (2) thrombotic microangiopathy

Infection-related GN

Primary diagnosis: IgA–dominant infection–related GN

Secondary diagnoses: diabetic nephropathy, moderate interstitial nephritis

Commentary/notes

PROBLEMS

- Lack of inter-observer and intra-observer reproducibility
- Lack of enough validation studies
- Usually non objective selection of study groups/testable lesions
- Lumps different lesions together
- Subjective qualification and scoring systems
- Lack of precise definitions
- When You Can't Classify

FUTURE APPROACHES "VISION"

Gene Expression Profiles

The challenge of functional genomics in pathology is to turn expression and sequence data into information that can be used to help diagnose disease

Laser-assisted microdissection allowed the evaluation of mRNA expression on material fixed and processed for routine diagnostic evaluation

Add on technique
applied to defined differential diagnostic problems after completion of the routine diagnostic work-up, e.g. FSGS vs Minimal Change

Integrated Diagnosis
Gene expression profiles performed in parallel to routine work-up of biopsies giving independent information in the diagnostic process using microarrays..high quality RNA

PROSPECTIVE

In the last decade

Tremendous advances have been made in our understanding of the pathology and pathophysiology of kidney disease as a result of intense collaboration between nephrologists and nephropathologists

Over the next years

The generation of comprehensive expression profiles for the most frequent renal diseases can be expected and may allow the definition of clinical subgroups with different disease courses


Thank You